REMARKS

1. History/Elections

Claims 1-9 are presently pending. Claims 10-108 have been withdrawn for prosecution at a later date.

The outstanding issues in the outstanding office action are addressed individually below.

2. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-9 were rejected under 35 U.S.C. § 112, first paragraph, as not enabling one of skill in the art to make and use the claimed invention (Office Action, pg. 3). Specifically, the Office Action states that the specification, while being enabling for *in vitro* blood cell lines, is not enabling for *in vivo* multidrug resistant protection (Office Action, pg. 3). The Office Action further alleges that Gehrmann *et al.* (2005) *Cell Stress Chaperones* 10(2): 136-146 ("Gehrmann") shows the unpredictability of diagnosing multidrug resistance because the Gehrmann shows that a decrease in cell surface-expressed Hsp70 occurred upon development of multidrug resistance (Office Action, pg. 4). Furthermore, the Office Action states that no correlation has been established between the *in vitro* data shown in the specification and *in vivo* multidrug resistance of primary tumors (Office Action, pg. 5). Applicants respectfully traverse this rejection.

According to MPEP § 2164.01, a claimed invention must be enabled so that any person skilled in the art can make and use the invention without undue experimentation. The fact that experimentation may be complex does not make it undue, especially if the art typically engages in such experimentation (MPEP § 2164.01). The test of enablement is not whether any experimentation is necessary, but whether it is undue (MPEP § 2164.01). Moreover, the quantity of experimentation is not undue "since a considerable amount of experimentation is permissible, if it is routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (MPEP § 2164.06; *quoting, In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988).

Enablement of a claimed invention requires a correlation between the *in vivo* or *in vitro* model used in the application and the disclosed method of use (MPEP § 2164.02). The issue of

correlation is dependent on the state of the art. If the prior art shows that a correlation exists between a particular model and a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate (MPEP § 2164.02). A rigorous or invariably exact correlation is not required where the disclosure of pharmacological activity is reasonable based upon the probative evidence (MPEP § 2164.02, *quoting* Cross v. Iizuka, 753 F.2d 1040, 1050 (Fed.Cir. 1985)).

Applicants assert that a correlation between cell lines and primary tumors *in vivo* is recognized in cancer research (see see, *e.g.*, Falzon *et al.* (2000) *Endocrinol.* 141(5): 1882-92; Gao *et al.* (2000) *Mol. Pharmacol.* 58(5): 1001-10). In particular, cancer researchers have long used cell lines to identify multidrug resistance markers that have been later identified in primary tumors in patients (see, *e.g.*, Kartner *et al* (1983) *Science.* 221(4617): 1285-1288 (identifying PgP protein in human tumor cell lines); Linenberger *et al.* (2001) *Blood.* 98(4): 988-994 (showing that PgP is associated with drug resistance in patients)). Furthermore, the Gehrmann reference utilizes cell lines in its studies and specifically refers to other studies showing that the results from the cell lines were similar to results obtained from patient-derived tumors (see Gehrmann *et al.*, pg. 144, *citing,* Gehrmann *et al.* (2003) *Haematologica* 88(4): 474-476). It is, therefore, apparent that cancer researchers have long accepted cell lines as a predictable and reliable model for *in vivo* primary tumor behavior.

Applicants also aver that the Gehrmann reference describes a study showing the relationship of cell surface expression of Hsp70 protein to treatment with retinoids and other vitamin A derivatives, but does not relate to **Hsc**70 protein (see Gehrmann *et al.*, pg. 137). Hsc70 and Hsp70 are not the same protein, but are isoform members of the HSC70 family (see Sens *et al.* (1997) *Eur. J. Oral Sci.* 105(3):271-7). They can be separately identified using isoform-specific antibodies (see *Id.*). In addition, Hsp70 and Hsc70 show different patterns of expression (see *Id.*). Thus, Gehrmann does not relate to the subject matter of the claimed invention, which is directed to measuring the levels of cell surface-expressed **Hsc**70 in test neoplastic cells to determine the test neoplastic cells are multidrug resistant.

Furthermore, Applicants respectfully assert that the specification provides sufficient guidance to allow one to practice the invention *in vivo.* The specification teaches that the test cell can be obtained from biopsy samples (see Specification, pg. 28, ll. 9-10). The Examples

teach non-limiting embodiments in which tissues from brain, blood, breast, ovary, and lung were isolated from patients and tested for cell surface expression of Hsc70 (see Examples 9 and 12). Exemplary embodiments showing the detection of cell surface-expressed HSC70 using two-dimensional electrophoresis and immunoblotting are also disclosed (see Examples 1 and 3). Moreover, the specification provides guidance on how to make and use labeled binding agents to measure cell surface-expressed HSC70 (see Specification, pg. 31, line 22-pg. 33, line 20). It also discloses specific Examples showing the use of anti-HSC70 antibodies as binding agents to detect cell surface-expressed HSC70 on resistant and nonresistant cancer cells (Examples 1 and 3). Therefore, one of skill in the art would be enabled to practice the claimed invention *in vivo* with only routine experimentation.

Accordingly, Applicants respectfully request that this § 112 enablement rejection be reconsidered and withdrawn.

Claims 1-9 were rejected as failing to comply with 35 U.S.C. § 112, first paragraph, for failing to describe the subject matter of the claimed invention in such a way as to reasonably convey to one of skill in the art that the inventors were in possession of the claimed invention at the time the application was filed (Office Action, pg. 5). More specifically, the Office Action contends that the specification discloses a genus of potential amino acid sequences because of the use of the indefinite article "an" to describe "an amino acid sequence of SEQ ID NO: 1" (Office Action, pg. 6). According to the Office Action, the specification fails to provide sufficient distinguishing characteristics for one of skill in the art to identify the genus (Office Action, pg. 6). Also, the Office Action alleges that the specification has not identified those regions of the protein that must be conserved in order for the invention to have its recited function (Office Action, pg. 6). Applicants respectfully traverse this rejection.

An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed" (see MPEP § 2163.02, *citing, In re Gosteli,* 872 F.2d 1008, 1012 (Fed.Cir. 1989). The subject matter of the claim need not be described literally in order for the disclosure to satisfy the description requirement (see MPEP § 2163.02). Also, the written description requirement may be satisfied by disclosure of structural chemical formulas or by describing distinguishing identifying characteristics sufficient to show that the

applicant was in possession of the claimed invention (MPEP § 2163; *see also Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68 (1998).

Applicants respectfully aver that the specification shows one of skill in the art that the Applicants were in possession of the claimed invention. As an initial matter, the specification provides the complete Hsc70 amino acid sequence (see Specification, pg. 12, lines 17-18). Additionally, the specification describes three sequences that were used to generate biotinylated sequences for identification of the Hsc70 protein in immunoblots and two-dimensional gel electrophoresis (see Figures 3, 5, and 6). The specification also discloses nine peptide sequences that were specific for Hsc70 (see Figure 6). One of skill in the art would immediately recognize that the amino acid sequences disclosed in the specification can be used to identify Hsc70. Thus, the specification provides one of skill in the art with explicit structural formulas of the full length Hsc70 protein and sub-sequences that can be used to identify Hsc70 using the claimed invention.

Moreover, Applicants assert that one of skill in the art, given the complete primary sequence of Hsc70, would know what regions of the protein were required for the methods of the claimed invention. Hsc70 is one of the most highly conserved proteins amongst all species (see, *e.g.*, Graser *et al.* (1996) *Genetica,* 98(3): 273-276). The Hsc70 protein has been isolated from bacteria, humans, zebra fish, and several mammals (see, *e.g.*, Graser *et al.* (1996) *Genetica,* 98(3): 273-276). The primary sequence can be used to identify cell surface-expressed Hsc70 utilizing the methods of the invention. The specification discloses the chemical sequence of Hsc70, which is highly conserved, and individual peptide sequences that can be used to identify Hsc70. Therefore, one of skill in the art does not require recitation of every Hsc70 sequence for adequate written description due to the high conservation of the protein across species and the recognition of such conservation in the art.

Accordingly, Applicants respectfully request that this § 112 rejection be reconsidered and withdrawn.

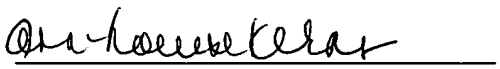
CONCLUSIONS

In view of the arguments set forth above, Applicants respectfully submit that the outstanding rejections contained in the Office Action mailed on August 1, 2006 should be reconsidered and withdrawn.

No additional fees are believed to be due in connection with this response. However, please charge any underpayments or credit any overpayments to Deposit Account No. 08-0219.

If the Examiner believes that any further discussion of this communication would be helpful, please contact the undersigned at the telephone number provided below.

Respectfully submitted,



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